CLINICAL STUDY

Clinical Experience with Trimethoprim - Sulfamethoxazole and Prednisolone in the Treatment of Ocular Toxoplasmosis with Zone -1 Posterior Pole and Peri-papillary Lesions

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Abstract

Objective

To evaluate the efficacy of trimethoprim- sulfamethoxazole and oral prednisolone in the treatment of ocular toxoplasmosis with zone-1 posterior pole and peri-papillary lesions.

Methods

Retrospective evaluation of records of patients in our tertiary care referral hospitals.

Results

22 eyes of 21 patients with active toxoplasma retino-choroiditis in zone -1 posterior pole and peri-papillary areas were included in the study. One patient developed active lesion in the fellow eye after 6 months which regressed after re-institution of the treatment.

There were 11 females and 10 males. Age varied between 18-52 (mean age 29±8.8) years. The follow-up period varied between 4- 46 (mean 15± 11) months. All patients showed resolution of retino-choroiditis and improvement of visual acuity between 1- 9 lines (mean 4.18 lines± 2.3).The mean lesion size pre-treatment was 0.89 disc diameters±0.3 and post-treatment was 0.70 disc diameters±0.28. The mean time taken for the sharpening of lesion borders was 2.3±0.4 (range 2-3) weeks. No complications reported with the medication.

Conclusion

The combination of trimethoprim-sulfamethoxazole and prednisolone is quite effective in treating the patients with active vision threatening posterior pole and peri-papillary toxoplasmosis lesions.

Key words: Toxoplasma retino-choroiditis, trimethoprim-sulfamethoxazole, posterior pole and peri-papillary lesions

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Introduction

Ocular toxoplasmosis is the most common cause of posterior uveitis world over [1,2]. The retino – choroiditis is as a result of actively proliferating organisms which can destroy the retinal tissue with resultant retinal scars which can affect the visual acuity irreversibly[3, 4]. Hence the goal of treatment should be to arrest the multiplication of the parasite in the active stage at the shortest possible time and thereby decreasing the risk for vision loss.

There are multiple treatment options available including the more commonly used traditional combination therapy with pyrimethamine, sulfadiazine and folinic acid rescue[5]. The other drugs being tetracyclines, clindamycin, spiramycin, atovaquone, azithromycine, trovafloxacine and trimethoprim-sulfamethoxazole.

A combination of sulfadiazine with pyrimethamine and corticosteroids is considered the most effective treatment for toxoplasmosis; however the cost of treatment, significant side effects, non-availability in certain locations, the necessity for their combination and frequent dosing made them less compliant [5-7] pyrimethamine has depressant effect on bone marrow and needs folinic acid rescue to reverse it. These patients have to be followed with weekly laboratory blood tests.

A less toxic means of treatment consists of clindamycin in combination with sulfadiazine for 4 to 6 weeks [8]. This combination was repeatedly shown to be effective in patients with ocular toxoplasmosis. Clindamycin has systemic side effects like skin rash, diarrhea and importantly psuedomembrane colitis which necessitate immediate interruption of clindamycin and institution of vancomycine or metronidazole therapy. Trimethoprim-sulfamethoxazole has similar mechanism of action as pyrimethamine and sulfadiazine. In addition they were found to have similar efficacy in their inhibitory effect on T.gondii infected HeLa cells [9]. Trimethoprim-sulfamethoxazole is readily available as a fixed drug combination and has convenient BID dosing. The combination is time tested and proved to be safe. Unlike pyrimethamine which needs mandatory periodical hematological evaluation, it is not performed routinely during trimethoprim – sulfamethoxazole therapy. In addition, it eliminates the need for folinic acid rescue [6,7]. Rothova *et al* [6] used trimethoprim-sulfamethoxazole for the first time in1989 in 8 patients, as a part of their prospective multicentre study of ocular toxoplasma therapies. Opremcak *et al* [7] reported clinical efficacy of trimethoprim-sulfamethoxazole therapy in 16 patients. Since then this combination therapy has been used with increasing popularity such that the use of this therapy has increased from 5 % in 1992 to 28 % in 2002[5, 10].

Recently [11] a major prospective randomized study has shown that the trimethoprim – sulfamethoxazole and prednisolone therapy is an acceptable alternative to the standard therapy by sulfadiazine- pyrimethamine and prednisolone in treating ocular toxoplasmosis. All the studies [6,7,11] done so far were unclear about the efficacy of the combination therapy by trimethoprim-sulfamethoxazole for the vision threatening posterior pole and peri-papillary lesions especially those that are involving fovea. Our aim was to review and evaluate our experience with fixed combination of 160mg trimethoprim and 800 mg sulfamethoxazole (Bacrim DS - Roche pharmaceuticals co.) and oral prednisolone in the patients with active zone-1 posterior retino - choroidal lesions threatening fovea and optic nerve.

Materials and Methods

The records of patients with active ocular toxoplasmosis in posterior pole and peri-papillary areas, who received fixed combination antibiotics in our tertiary care referral hospitals (Magraby Eye Centre and King Abdul Aziz University Hospital) from January 2002 to May 2006, were analyzed retrospectively. The main outcome measures were clinical resolution of active retino-choroiditis, visual out come and safety profile of the medication. All the patients underwent standard ocular evaluation including ocular and medical history; best

corrected visual acuity, slit lamp biomicroscopy and dilated fundus examination. The diagnosis of ocular toxoplasmosis was based on the clinical findings. All our cases had typical reactivation of congenital toxoplasma scars. However, Enzyme-linked immunosorbent assay (ELISA) was done for all the patients for Ig G and Ig M antibodies with undiluted serum.

The active lesion of retino-choroiditis was documented in retinal diagrams in relation to macula and optic nerve. The patients were categorized according to the location of the lesion. The lesions with in temporal arcades or 2 DD temporal to fovea and away from 500 microns of foveal centre were considered as macular lesions. The lesions involving or with in 500 microns from foveal centre were considered as foveal lesions. The lesions with in 2 DD from optic nerve head were considered as Peri-papillary lesions.

The activity was judged by the appearance of the lesion with respect to the pigmented scar, the color and the margin of the lesion, presence and absence of retinal hemorrhages, presence and absence of vitreous cells. The anterior vitreous inflammation was graded according to the standard system devised by Kimura et al.[12] The size of active lesion was measured clinically in disc diameters. The inactive adjacent scar was excluded in measurement. All these parameters were studied in subsequent follow-up visits i.e., 2 weeks, 3 weeks, 4 weeks and 8 weeks. The time taken for the sharpening of lesion borders and resolution of vitreous inflammation noted.

All patients were treated with 160 mg trimethoprime and 800 milligram of sulfamethoxazole, for a minimum period of 4 weeks. The lesions affecting the foveal centre were treated for six weeks. Prednisolone tablets 1/2 mg per kg body weight was given to all patients 48 hours after starting the first dose of 160 mg trimethoprime and 800 mg of sulfamethoxazole and tapered slowly for 2 weeks for extra- foveal lesions and for 3 weeks for foveal lesions. The patients who were allergic to sulfa were excluded. We did look for G6PD deficiency in our patients; however all of them were advised to observe the changes of urine color, and to report to us immediately.

Recurrence was defined as the active lesion as documented clinically after four weeks of inactivity. The patients with inadequate follow-up (i.e., less than 4 months) were excluded from the study.

Results

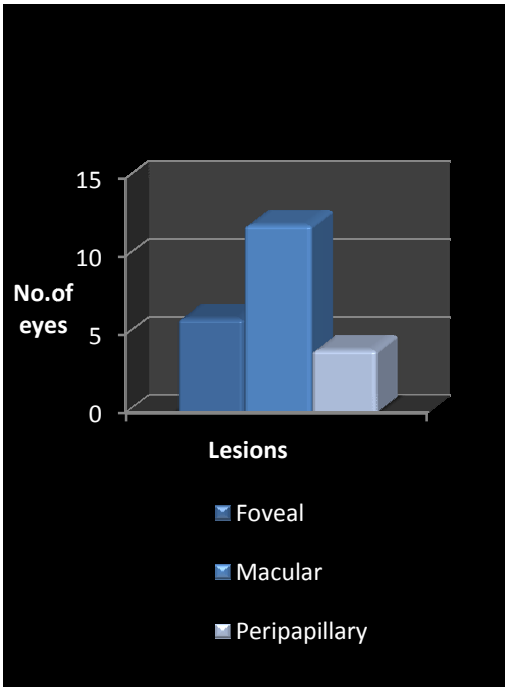
Retrospective study of records of the patients from our tertiary medical centers revealed a total of 38 patients with toxoplasma retino-choroiditis. Among them 4 patients received clindamycin and were excluded from the study. Among the remaining 34 patients who received trimethoprim- sulfamethoxazole therapy, 11 patients had extra macular lesions and hence excluded from the study. Among the remaining 23 patients 2 patients lost to follow-up after initial treatment. The remaining 21 patients with active toxoplasma retino-choroiditis lesions that were located in posterior pole and peri-papillary areas were included for our study. One patient developed active foveal lesion in his fellow eye 6 months after institution of treatment however, showed regression of the lesion after re-institution of the treatment. Hence we analyzed 22 eyes of 21 patients (**Table 1**).

All our patients had retinal scars. There were 11 females and 10 males. Age varied between 18-55 years.(mean 29.12$\pm$ 8.8 years). The Macular lesions and Peri-papillary lesions were treated for 4 weeks. The Foveal lesions were treated for 6 weeks. The follow-up period varied between 4- 46 months (mean 15 $\pm$ 11 months) **.** There were 12 eyes with macular lesions, 6 eyes with foveal lesions and 4 eyes with nasal peri-papillary lesions. (**Figure 1**). All the foveal lesions were encroachments from the parafoveal lesions (macular) and none involved the foveal centre.

All patients showed resolution of retino-choroiditis resulting in inactive scars. The time taken for the lesions to show sharpening of borders ranged from 2 to 3

weeks (mean 2.3 ± 0.47 weeks). The larger lesions (>1.0 DD) took more time (3 weeks) to show sharpening than smaller lesions. The retino-choroidal lesions showed decrease in size after treatment in 16 out of 22 eyes. The size of the lesion was stable in 5

Figure 1: The location of the lesions



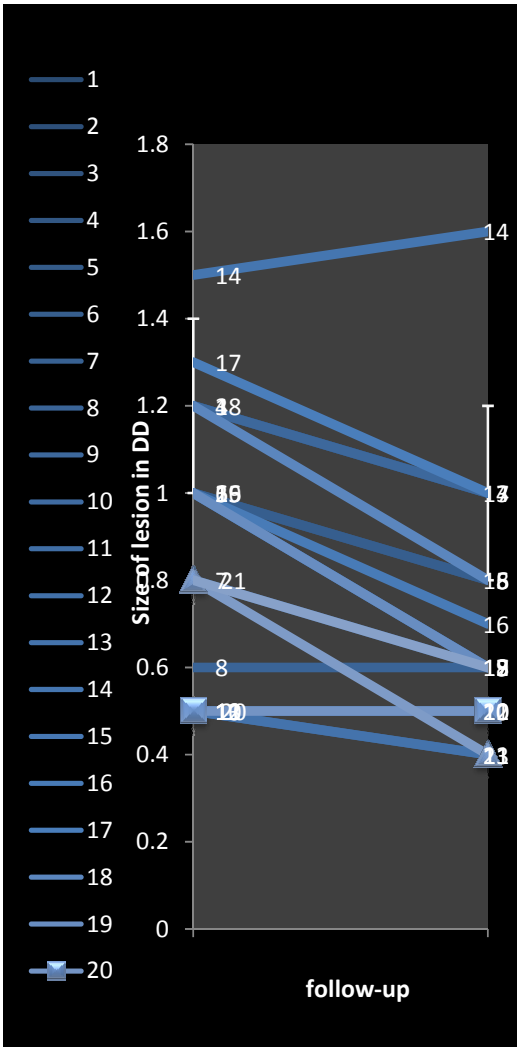
eyes. In patient No 14 (**Table 1, Figure 2**) macular lesion showed increase in the size during treatment and encroached the foveal zone (500 microns of foveal centre) partially without involving the foveal centre: however regressed completely at the end of 6 weeks. The mean lesion size pretreatment was 0.89 ± 0.32 DD (range 0.5 – 1.5 DD) and post treatment was 0.7 ± 0.28 DD (range 0.4 – 1.6 DD).

Anterior vitreous inflammation was noted in all the patients that ranged from 1+ to 2+ cells. 15 out of 22 (68 %) eyes showed trace to absence cells after 2 weeks .The remaining 7 (32 %) eyes took 3 weeks. The resolution of anterior vitreous inflammation roughly corresponded to the sharpening of lesions borders. No complications reported with the medication. There were no recurrences in the treated eyes till the last follow – up visit.

Discussion

The ocular toxoplasmosis can cause irreversible loss of vision if it involves the critical areas such as fovea and optic nerve, hence the need to treat them with the most potent and reliable medication with sufficient dosage so as to limit the retinal scarring and visual loss.

Figure 2: The change of lesion size in disc diameter



Lesion size -eyes
Increased- 1
Decreased- 16
Stable - 5

Table 1. Details of patients' characteristics, pre & post treatment (Pre / Post) visual acuity and lesion size, time taken for the sharpening of lesion border (T-sharp of LB) and follow-up.

No	Age	Sex	Eye		Pre lesion Size (DD)	VA pre	Location Of lesion	VA Post	Post lesion Size (DD)	T-sharp LB (weeks)	Follow up period (month)
1	18	F	OD		0.5	20/30	Peripapillary	20/20	0.5	2	11
2	22	M	OS		1	20/60	Macular	20/20	0.6	2	9
3	27	F	OD		1.2	20/800	Macular	20/80	1.0	3	9
4	32	F	OD		1.2	20/100	Macular	20/20	1.0	3	11
5	25	M	OS		1.0	20/100	Macular	20/25	0.8	2	12
6	35	M	OD		1.0	20/600	Foveal	20/120	0.8	2	9
7	42	F	OD		0.8	20/60	Macular	20/20	0.6	2	9
8	36	M	OD		0.6	20/30	Macular	20/20	0.6	2	8
9	25	M	OS		1.2	20/120	Macular	20/60	1.0	2	8
10	50	F	OD		0.5	20/100	Macular	20/30	0.5	2	42
11	24	F	OS		0.5	20/25	Peripaillary	20/20	0.4	2	36
12	26	F	OD		0.5	20/100	Macular	20/60	0.5	2	46
13	23	F	OD		0.5	20/30	Peripapillary	20/20	0.4	2	10
14	22	M	OS		1.5	20/800	Foveal	20/600	1.6	3	12
15	38	M	OD		1.0	20/400	Foveal	20/100	0.6	2	18
16	21	M		OD	1.0	20/600	Foveal	20/400	0.7	2	4
16	21	M	OU	OS	1.3	20/120	Macular	20/60	1.0	3	10
17	29	F	OD		1.2	20/200	foveal	20/60	0.8	3	12
18	33	M	OS		1.0	20/40	Macular	20/20	0.6	2	14
19	40	M	OS		0.5	20/30	Peri-papillary	20/20	0.5	2	12
20	52	F	OS		0.8	20/80	Macular	20/20	0.4	3	14
21	39	F	OD		0.8	20/400	Foveal	20/100	0.6	3	14

The established treatment for ocular toxoplasmosis has been the combination therapy with sulfadiazine and pyrimethamine for the past five decades[13]. The non availability of these combinations in certain locations, the frequent adverse reactions and the need for their hematological monitoring has forced the clinicians to look for alternative drugs with almost equivalent efficacy and reliability[5,7]. Although, trimethoprim - sulfamethoxazole is therapeutically equivalent to sulfadiazine –pyrimethamine, clinically it was speculated to be inferior. [6] The use of these agents in treating vision threatening posterior pole and peri-papillary lesions without adjunctive treatment was never established. Rothova *et al* [6] used trimethoprim-sulfamethoxazole for the first time in 8 patients. Opremcak et al [7] used the fixed dose of the trimethoprim-sulfamethoxazole combination therapy in treating toxoplasmosis retino-choroiditis lesions. They categorized the patients according to location of lesions as described by Holland *et al*[14]. Zone-1 lesions were considered as the lesions located with in temporal arcades (2 disc diameters from the fovea)

or 2 disc diameters nasally from the optic nerve head. Zone 2 lesions are the lesions anterior to zone 1 and within clinical equator demarcated by anterior borders of vortex veins ampullae. Zone 3 lesions are anterior to zone 2 till ora serrata. The patients with zone 1 lesions and the other lesions with severe inflammation and opacified vitreous were treated with fixed dose combination of trimethoprim and sulfamethoxazole along with adjunctive therapy with clindamycin and oral prednisolone .The other zone 2 and 3 lesions did not receive the adjunctive treatment. The Zone 1 lesions received adjunctive therapy because they were adjacent to macula and optic nerve. Opremcak *et al* were unclear about the efficacy of the trimethoprim-sulfamethoxazole alone in treating these lesions.

Recently Sohelian *et al* [11] in a major prospective randomized study comparing standard therapy with sulfadiazine-pyrimethamine to the trimethoprim-sulfamethoxazole therapy concluded that drug efficacies in terms of reduction in retinal lesion size and improvement in VA were similar in both regimens. However, they excluded the lesions involving 500 microns with in fovea. Hence the role of trimethoprim-sulfamethoxazole in treating these critical lesions has not been studied.

In our study, we attempted to treat the posterior pole and peri-papillary lesions with the trimethoprim-sulfamethoxazole therapy along with oral prednisolone. We followed our patiently more closely i.e., 2 weeks , 3 weeks ,4 weeks and 6 weeks . All our patients showed resolution of the active disease without any adverse effects and recurrences.

The treatment of toxoplasma induced retino - choroiditis is aimed to decrease the size of inflammatory mass and hence to limit the resulting the retino-choroidal scar. Sohelian et al [11] noted a mean reduction of 59% in the retinal lesion size which was similar (61%) to pyrimethamine - sulfadiazine therapy. Rothova *et al* [6] noted significant reduction of retinal lesion (defined as at least half a disc diameter reduction in diameter) in 11 % of patients receiving the trimethoprime-sulfamethoxazole treatment which was significantly less than the response with pyrimethamine-sulfadiazine combination (49 %).

Rothova *et al* [6] used trimethoprim – sulfamethoxazole in full dose (960- mg twice daily) for only 2 weeks. They used the half the dose (380 mg twice daily) for the remaining 2 weeks. In our study we used 960 mg trimethoprim-sulfamethoxazole twice a day for 4 weeks. The patients with foveal zone disease received 6 weeks therapy.

All the lesions were either stable (5 eyes) or showed decrease in size (16 eyes) of the active lesion during the treatment period except for one patient (pt.no.14) with Macular disease (Figure 2) which showed mild increase to involve the foveal zone however showed regression after prolongation of treatment duration to 6 weeks. The mean pre-treatment size of active lesions was 0.89 $\pm$ 0.32 DD (range 0.5 to 1.5 DD) and post - treatment was 0.7 $\pm$ 0.28 DD (range 0.4 to 1.6 DD). We measured the size of active lesion in disc diameters excluding the surrounding inactive scars.

The authors did not calculate the percentage reduction of the lesions size as we believe in suggestion of Holland[15] that the time taken for the sharpening of lesion borders along with resolution of vitreous inflammation are far better indicator of the efficiency of treatment modality than the percentage decrease of retinal inflammatory lesion size as it ultimately leads to retinal scar. In our study, the average time for the sharpening of lesion border was 2.3 $\pm$ 0.47 (range 2-3) weeks. The time required for a retino-choroidal lesion to heal varies depending upon the size of the lesion, the treatment modality and the immunological condition of the host and the strain[6,16,17.] In our study the larger lesions > 1.0 DD took more time (3 weeks) to show sharpening of lesion border than the small lesions (< 1.0 DD).

Sohelian *et al* [11] noted 56.7 % of the patients showing improvement of vitreous inflammation after treatment with trimethoprim-sulfamethoxazole which was similar to the treatment with classic pyrimethamine-sulfamethoxazole therapy

(69%). However, they have not mentioned the time taken for the resolution of the inflammation (trace to absence cells). In our study the eyes with smaller lesions were also the eyes which became quieter earlier than the eyes with larger lesions. 15 (68%) eyes showed improvement of anterior vitreous inflammation with in 2 weeks and the remaining 7 (32 %) eyes took 3 weeks to show trace/absence of cells. The time taken for resolution of vitreous inflammation corresponded with time taken for the sharpening of lesion border and both depended upon the initial size of the lesion. As we mentioned earlier, the time taken for sharpening of lesion border and resolution of vitreous inflammation are better indicators of the efficacy of treatment.

Sohelian *et al* [11] reported five lines improvement of snellens lines with trimethoprim-sulfamethoxazole therapy which was similar to that of pyrimethamine-sulfamethoxazole therapy (5.5 lines.) Similarly Opremack *et al* [7] showed improvement of 5.2 lines in their patients. In our study, we noted 4.1 lines of improvement of visual acuity. This can be explained by the fact that all our patients had vision threatening macular and peri-papillary lesions and 6 patients with foveal lesions. The vision improved in all patients including those who had foveal lesions. We speculate that the chemo-reduction of active lesion could have resulted in a much smaller scar sparing the surrounding zone of photoreceptors. However, there is no study supporting this hypothesis

The great majority (80- 90 %) of ocular toxoplasmosis was believed to occur as a consequence of reactivation of congenitally acquired infection. An isolated and solitary and active lesion without previous retinal scars was considered as acquired infection[15]. A study from Iran [11] noted 50.8 % of their patients without retinal scars suggesting of having had acquired infection. Furthermore, they observed that these patients with acquired disease were showing better response to pyrimethamine-sulfadiazine therapy than with the Trimethoprim - sulfamethoxazole. In our study all our patients had retinal scars and hence had congenital infection and showed good response by the use of trimethoprime-sulfamethoxazole. The congenital ocular toxoplasmosis may be more effectively treatable with the use of trimethoprim-sulfamethoxazole than acquired disease. This needs to be confirmed by further study.

As all the available drugs including the trimethoprim-sulfamethoxazole regime, are incapable of eradicating the latent tissue cysts, recurrences were observed with all treatment modalities [17]. Opremcak *et al* [7] encountered 3 recurrences in one patient. Sohelian *et al*[12] noted 3 recurrences in the trimethoprime and sulfamethoxazole treatment group and similar recurrences with sulfadiazine-pyrimethamine therapy. We did not encounter recurrences in any of treated eyes during our follow up period that ranged from 4 to 46 months. In view of our limited follow-up we are unable to comment on the recurrences.

The Medline search did not reveal occurrence of simultaneous bilateral active toxoplasmosis lesions in immuno-competent persons. Moshfegi *et al*[18] noted atypical widespread active bilateral toxoplasmic retinochoroidits in a HIV patient. How ever there is a possibility of fellow eye getting active disease during follow up as happened to one of our patient No 16 **(Table 1**) who developed active foveal lesion in the fellow eye (OD) 6 months after the institution of trimethoprim-sulfamethoxazole therapy. This patient showed regression of the lesion after re-institution of the trimethoprim-sulfamethoxazole therapy. This may be considered as recurrence of the disease in the fellow eye considering the systemic nature of the therapy.

The trimethoprim and sulfamethoxazole combination therapy has been used for prophylaxis against toxoplasma induced encephalitis in AIDS patients in 1992 [19]. The long term intermittent trimethoprim-sulfamethoxazole treatment was shown to prevent the recurrences in ocular toxoplasmosis [20].

Opremcak *et al* [7] noted mild rash, colitis and headache in 2 patients each. Sohelian *et al* [11] noted mild rash in one patient. All our patients did not complain any of these

adverse events. This suggests well tolerability of this combination in our part of the world.

The systemic corticosteroids are necessary to contain the necrotizing inflammatory process which can damage the visually sensitive areas like macula and optic nerve. The treatment with steroids is usually delayed by 12 - 48 hours after institution of anti-toxoplasma treatment to achieve therapeutic levels of the drug and usually tapered 2 weeks before the discontinuation of the treatment. All our patients received oral prednisolone (1/2 mg per kg body weight) 48 hours after the institution of initial dose and slowly tapered for 2 weeks for extra- foveal lesions and tapered for 3 weeks for foveal lesions. We did not use the higher dose of steroids as we wanted the anti- inflammatory effect only. In addition to contain inflammatory mass size the corticosteroids also aid in reducing the accompanying vitritis, cystoid macular edema and the retinal vasculitis.

Active toxoplasma retinochoroiditis is a self limited disease for which there is inadequate evidence to support the routine use of antibiotics[21]. How ever, considering the consequences of irreversible loss of vision by untreated active posterior lesions especially involving fovea and optic nerve and the suggestive evidence that the treatment can reduce the resultant retinal scar[6], it seems reasonable to treat the active toxoplasmosis lesions with safe and effective medication with the least side effects.

The results of our study show that trimethoprim - sulfamethoxazole therapy along with oral corticosteroids appears to be effective and sufficient in treating ocular toxoplasmosis even in vision threatening lesions. This may obviates the need for other adjunctive drugs like clindamycin, thus lessening the cost, minimizing the adverse effects and improving patient compliance. How ever, there is a need for a prospective, randomized control study to test the efficiency of combined use of trimethoprim - sulfamethoxazole therapy in treating the vision threatening posterior pole and peri-papillary lesions with respect to the natural course of untreated disease and with respect to established treatment modalities with drugs such as sulfadiazine-pyrimethamine and clindamycin.

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Note:
Authors do not have proprietary interest in any of the drugs mentioned in this article.